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Comment

Future of Laser Dermatology

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Background and Objective: **Laser dermatology, a long-time model for laser tissue interactions, will play an important part in the future of research, diagnostics, and therapeutics.**
Study Design/Materials and Methods: **Laser research continues in photobiology, especially in molecular reactions, and it continues at the cellular level in melanocyte and Langerhans cells.**
Results: **Laser diagnostics in the development of opto-electronics concern new developments in imagery. Some studies include new types of microscopes for living skin and vary from the portable illuminated skin microscopes, the current dermatoscopes, to the coaxial polarizing microscope and the new scanning confocal microscope of Gmitro for living tissues. The regular confocal microscope for fixed tissue slides will revolutionize dermatopathology. The other research microscopes include the ultrasonic biomedical microscope and the IR microscope and the holographic microscope of optical phase conjugation used for living tissues.**
Conclusion: **New lasers for therapy include micromedical lasers, economical junction diode lasers alone and for pumping solid-state lasers, FEL of the future, and multiwavelength laser units. These later units include seven-wavelength units of barium, copper vapor and ruby, and are available for other heavy metal laser heads, ds gold-628 nm and lead-722 nm. Copper vapor can pump also Ti sapphire. The MOPO series (200 nm in the UV to > 4,500 in the IR) is the most extensive modern multiwavelength laser box type. Lasers Surg. Med. 22:3–8, 1998.** **© 1998 Wiley-Liss, Inc.†**

Key words: laser diagnostics; microscopies; multiwavelength lasers; melanocyte cells; langerhans cells

INTRODUCTION

Laser dermatology began in 1961 [1–7], and its medical and surgical applications have continued to progress along several lines including research, diagnostics, and therapeutics. Current research in dermatology has made significant progress in the development of confocal scanning microscopy for the diag of early melanoma. What new research and applications can we imagine for the laser dermatology of the future? The objective of this article is to provide some insights into future concerns in laser dermatology in new research areas, diagnostic techniques, and therapeutic applications.

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LASER RESEARCH

In laser research, it is imagined that photobiologic effects will be studied at the subcellular level, perhaps even at the molecular level. Basic biologic mechanisms at the cellular level that are important to dermatologists would concern the behavior of melanocytes, particularly in their earliest evolution toward melanoma, and the behavior of Langerhans cells in their immunologic roles in the skin. With the advent of the x-ray laser, the skin provides a readily accessible and observable test model system for laser-tissue interactions concerning molecular holography and photosynthesis.

Interest continues in the melanocyte, especially for early changes from solar effects and in studies of solar nevogenesis by Stefanato et al. [8]. For the Langerhans cell, Bergfelt [9] recently has reviewed the significant features of presentation by this cell to T-lymphocyte defense against nevoantigens in tumors. She includes also effects of aging and drugs. She states that "long-term sun exposure or PUVA treatment is not associated with a permanent depletion of Langerhans cells." Significant pictures of Langerhans cells are shown, including confocal scanning microscopy in vertical sections of the epidermis. Cells and their dendrites are seen in the dermis in a basal cell carcinoma.

LASER DIAGNOSTICS

On the diagnostic frontier, skin imagery and especially subsurface imagery are at the forefront. The details of other areas of laser diagnostics are shown in Table 1. With regard to imagery, the skin surface has been studied with everything from the simple ancient magnifier to the most sophisticated scanning electron microscope [10]. Some of the most interesting pictures have been the scanning surface "electric" microscopy of Nilsson [10]. Two of his examples at very low magnification (45×) are a detailed photomicrograph of the Aedes mosquito taking its blood meal through the skin and a picture of the spermatozoa entering the ovum to start the process of conception.

Currently, common instruments used for magnified surface and subsurface imagery of living skin include: (1) the new dermatoscopes with all their accessories, (2) the coaxial polarizing microscope, (3) the IR microscope, (4) the ultrasonic biomedical microscope (UBM), (5) the confocal scanning microscope for microscopy of living skin, and (6) the new holographic optical phase conjugation microscope [11,12]. As a result of this exciting renaissance in optical technology, in vivo study of the normal and pathologic skin should become a fertile area of future research. For example, the details of the topography of living skin, particularly pigment distribution on the surface and below the surface of the skin. Although transillumination and the recent use of the dermatoscope have provided some information for help in diagnosis, additional developments of technology are necessary. Some of these factors are monochromatic versus polychromatic light sources, polarized versus unpolarized light with vertical versus oblique direction of polarization, vertical versus angulated direction of illumination, phase conjugation versus other nonlinear types of optics, and direct transillumination ver-

TABLE 1. Outline of Laser Diagnostics

I. Basic photobiology
II. Imagery
  A. Transillumination: all phases for surface and deep
  B. Chromophores: research and development
  C. Fiberoptics
  D. Instrumentation for living skin imagery
    1. Surface and subsurface
      a. Magnifiers
      b. Portable with moderate magnification
        - dermatoscopes
        - control portable scopes—10–35×
      c. Special microscopes
        - coaxial polarizing microscope
        - ultrasonic biomedical (UBM)
        - scanning confocal microscope
          / fixed section
          / living skin
        - IR microscope
        - holographic microscope with optical phase conjugation
      d. Special for fingerprint diagnostics
  E. Spectroscopy
    1. Toxicology
      a. Arsenic: medical/legal
      b. Lead: hair assays in children
    2. Cardiology: atheroma
    3. Oncology: carcinoma of the breast (Alfano)
  F. Studies of circulation
    1. Doppler: including intracellular
    2. Pulsed thermal radiometry (Nelson portwine marks)
    3. Evaluation of skin tests
  G. Sensors
    1. Pressure
    2. Thermal
    3. Chemical reaction
    4. Surveillance
    5. Electrical activity (cardiology)
    6. Biosensor lightning (lightning bugs: marine bacteria)
  H. Enzymology
    1. NADH fluorescence (ischemia in cardiology)

sus subsurface fiberoptic transillumination. All of these many factors are used in an attempt to recognize the earliest pathologic changes in skin, especially the living skin.

The Dermatology Department of the San Diego Naval Medical Center has a protocol for dermatoscopy to be utilized both as a critical study of evaluation and as a teaching program for residents in dermatology [13,14]. The consultant in dermatoscopy is Armand Cognetta, Jr., an experienced dermatoscopist [Cognetta Jr., pers. comm.]. Presently, the important control for the dermatoscope is the coaxial polarizing microscope (Zeiss). To have some flexibility for clinical examination with this polarizing microscope, it is attached to a movable support for easy access to the clinic. The other microscopes used for examination of the living skin are primarily for research studies in the future.

Some of our current studies concerned with subsurface imagery are to observe the melanocyte cell as this cell, in the living skin, reacts to solar radiation 1 hormona 1 influences or other reactions. For example, what happens to the patient at high risk for melanoma after a severe sunburn? Can we see any changes in or about the melanocytes? Do our diagnostic techniques change these cells? Can we detect subtle biochemical changes in cell surface markers at a molecular level without disturbing the cells themselves? Do we have exogenous chromophores to detect changes in pathologic cells of the epidermis or dermis?

One of the most fertile clinical fields for the use of endogenous and exogenous chromophores is in photodynamic dye therapy (PDT). We have been involved in PDT both for systemic use of the cellular chromophores and also for experimental topical use. Not only are the chromophores of interest for cancer diagnosis and treatment in the skin, but they have potential for the detection of various infections and even for parasitic infestations [15–19]. We agree with J.W. Steger [pers. comm.] that the confocal scanning microscope, with its laser, can follow the path of the fluorescent chromophore.

The dynamics of circulation including the microcirculation and intracellular circulation of specific metabolites should provide interesting problems for laser technology to solve. Of the current enzyme systems currently under study, the induced fluorescence of NADH is the most important for cardiovascular studies. With contrast injection, the fluorescence of NAH/NAD ratio is used to detect transient ischemia. The nucleotide coenzymes NADH are highly fluorescent at 340 nm and 450 nm. A laser fluorometer is used [20–21]. Other diagnostic techniques of interest to dermatology are found in Table 1.

An additional bit of information about the future of NADH is that a new fluorescence monitoring of NADH has been developed according to R. Stewart [pers. comm.]. A multiwavelength, dye-free laser uses a nitrogen laser pumped optical parametric oscillator to produce 337 nm, 586 nm, and 805 nm laser light, coaxilly and simultaneously. This system will soon be tested for PDT and for hyperthermic dosimetry. Also, such a system can be used noninvasively for melanoma detection [Stewart, pers. comm.].

With respect to biophysics and biochemistry of the skin, new applications continue for laser nonsurgical diagnostics in investigative dermatology.

LASER SURGERY

What are the imagined future developments in laser surgery, microsurgery, and the new intracellular surgery? The currently available laser systems for surgery will continue with miniaturization, increased flexibility, increased output, more Q-switched models, decrease in the basic cost of the instruments, and service contracts. One such example of miniaturization was an 81 mW Nd:YAG powered by a single AA battery developed by M. Muckerheide [pers. comm.] for our use on small blood vessels and for tattoos. This microlaser is also used for the treatment of glaucoma in ophthalmology. Since laser instrumentation is always progressive, what do we imagine for new systems in laser surgery? R. Rox Anderson [pers. comm.] believes that small economical diode lasers will be used at a variety of wavelengths by themselves. As their power is increased, they may be further used to pump solid-state laser systems—an important group of the future. We have observed the development of the free-electron beam laser from its early days. Ali Javan [pers. comm.] has told us that perhaps in the future we will have a desk model free-electron laser with tunability.

Another phase of laser development is the attempt to offer multiple frequencies and multiple laser instruments in one or two systems in one area. There are several examples of these multiple wavelength units currently available, such as the tunable dye lasers pumped by argon lasers. Increased wavelength versatility may include quasi CW dye with Wd: YAC,532 or 1,064 as

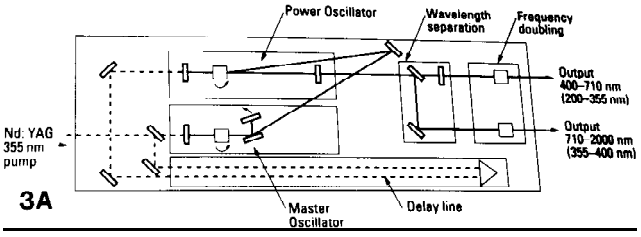

Fig. 1. The coaxial polarizing microscope for studies of pigmentation and vascular patterns.

Fig. 2. The 7 multiwavelength laser systems for dermatology. **A.** Copper vapor laser—511 nm; 578 nm; 511 with 578 nm. The ruby laser head sits on top of the copper vapor laser; ruby laser 694.3 nm. **B.** The barium vapor laser—1,500 nm; 11,300 nm; 1,500 with the 11,300 nm; other metal vapor laser heads can be attached easily here.

Fig. 3. **A.** Outline of the MOPO system for multiwavelength lasers. **B.**The optical parametric oscillator system of the future for biomedicine (Spectra Physics, San Jose, CA).

pump laser, krypton 521, 530, and 568, pulsed dye 510 nm and Q-switched alexandrite, 755 nm [J.W. Steger, pers. comm.]. Titanium sapphire units offer another example. Another, more versatile approach is the use of interchangeable metal vapor lasers to drive interchangeable solid-state modules. These lasers deliver nanosecond pulse widths without Q-switching. Under the direction of Steger [pers. comm.], the first of these interchangeable systems is currently being installed here in the Department of Dermatology. It includes seven wavelengths: (1) a copper vapor laser (CVL) operating at 511 nm, 578 nm, and 511 + 578 nm, (2) a ruby crystal external module, pumped by the copper vapor laser and delivering 40–60 nanosecond pulses at 5–15 kHz at 694.3 nm through an optical fiber, and (3) a barium vapor laser operating at 1130 nm, 1500 nm, and 1130 nm + 1500 nm.

Other metal vapor lasers include the gold vapor laser operating at 628 nm and a lead vapor laser operating at 722 nm. Interchangeable solid-state modules currently envisioned will include the ruby crystal, a tunable titanium sapphire crystal, and alexandrite crystals. The interchangeable use of heavy metal vapor laser heads for direct use or for pumping and the interchangeable solid-state modules provide the potential for a wide variety of fiberoptic deliverable frequencies. Further refinements in power output and computer controlled alterations in the pulse frequency and sequencing may yield a wealth of usable modes of operation for clinical problems, e.g., for pigmentary problems, the copper vapor laser at 511 nm, the gold vapor, barium vapor laser at 1,130 nm or lead vapor laser could be utilized; for tattoos, the barium vapor at 1,130 nm, the lead vapor at 722 nm, the copper vapor pumped ruby/alexandrite titanium sapphire; for cutting, the barium vapor at 1,500 nm or 1,130 + 1,500 nm; and for vascular lesions, the copper vapor at 578 nm ± Hexascan computerized delivery system. Optimization of pulse peak power, pulse width, pulse frequency, and computerized enveloping of groups of ultrahigh frequency (> 100 kHz) pulses are necessary for this group of laser systems. Barring the development of a continuously variable tunable wavelength, continuously variable tunable pulse width and frequency, and continuous variable tunable pulse power, these metal vapor lasers may offer a satisfactory and rather economical approach to a variety of clinical problems in dermatology.

A recent development of this multiwavelength system is the use of the "heart of this system," the copper vapor laser by Stewart [pers. comm.] to pump Ti:Sapphier and the NdYAG. The Ti:Sapphier is "seeded" with the output from a copper vapor laser pumped ruby crystal output to 694 nm. Stewart [pers. comm.] indicates that the average output from these crystals is at least 2 W. Selective wavelength is completely automatic. The output of 511 is 7 W with 3 W at 578. Therefore, for the future this system will have increased output for the applications listed above and also for the PDT malignancies.

Another interesting area of multiwavelength lasers is the Master Oscillator Power Oscillator (MOPO) systems suggested by our laser consultant, R. Scheps [pers. comm.], at the Naval Ocean Systems Center. The MOPO system can be upgraded in energy and line width area and extended in wavelength from 200 nm in the UV to 4,000 in the IR with energies of 100 mj. This system has great potential for biomedical applications. It is in the research laboratory stage by Spectra Physics (San Jose, CA). The laser used at the Naval Medical Center is the third harmonic of Nd YAG. Another similar research system of parametric oscillators is Continuum's second harmonic of Nd YAG in the second harmonic, green, with lesser number of multiple wavelengths. Coherent is also doing research on parametric oscillators. Parametric oscillators for NADH is mentioned above [R. Stewart, pers. comm.]. Current laser manufacturers are answering our plea for multiwavelength laser systems in a single unit. Again, laser biomedical engineers will help to develop reliable biomedical instrumentations, and laser safety experts will develop the complex laser safety programs. Dermatology will do the research and development for laser medicine and surgery and will develop the new laser safety program [R. Rockwell Jr., pers. comm.].

CONCLUSIONS

The skin will continue to be an important test organ for surface and subsurface imagery, diagnostics, and therapy. Therapeutic instrumentation on the skin is expanding and selectivity is increasing. With proper controls in the investigative and clinical areas, the future of lasers in dermatology continues to be bright.

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